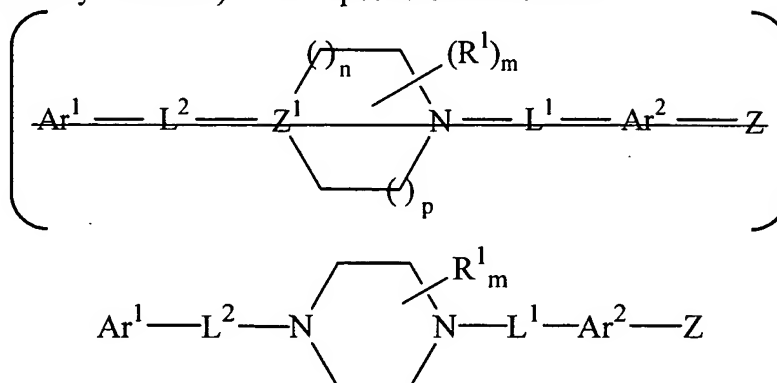


## CLAIM AMENDMENTS

1. (currently amended): A compound of the formula:



~~[[and]]~~ or the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein:

Ar<sup>1</sup> is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

$L^1$  and  $L^2$  are linkers;

each R<sup>1</sup> is independently a noninterfering substituent;

~~Z<sup>1</sup> is CR<sup>2</sup> or N wherein R<sup>2</sup> is hydrogen or a noninterfering substituent;~~

m is 0-4;

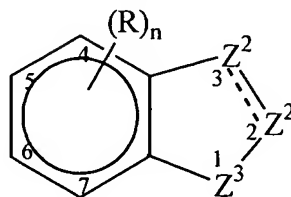
~~each of n and p is an integer from 0 2 wherein the sum of n and p is 0 3;~~


Ar<sup>2</sup> is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is  $-W_i-CO-X_jY$  wherein Y is  $COR^3$  or an isostere thereof;  $R^3$  is a H or a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of Ar<sup>1</sup> bonded to L<sup>2</sup> to the atom of Ar<sup>2</sup> bonded to L<sup>1</sup> is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of Ar<sup>1</sup> bonded to L<sup>2</sup> and the atom of Ar<sup>2</sup> bonded to L<sup>1</sup> is 4.5-24 angstroms; is no more than 24 angstroms;

with the proviso that the portion of the compound represented by  $\text{Ar}^2\text{-Z}$  is not



wherein  represents a single or double bond; n is 0-3; one  $\text{Z}^2$  is CA or CRA and the other is CR,  $\text{CR}_2$ , NR or N; A is  $-\text{W}_i\text{-COX}_j\text{Y}$  wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6Å, and each of i and j is independently 0 or 1;  $\text{Z}^3$  is NR or O; and each R is independently hydrogen or a noninterfering substituent.

2. (canceled)

3. (original): The compound of claim 1 wherein Z is  $\text{COX}_j\text{COR}^3$ , and wherein  $\text{R}^3$  is H, or is straight or branched chain alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, or heteroarylalkyl, each optionally substituted with halo, alkyl, heteroalkyl, SR, SOR,  $\text{SO}_2\text{R}$ ,  $\text{SO}_2\text{NR}_2$ , OR,  $\text{NR}_2$ , OCOR, NRCOR,  $\text{NRCONR}_2$ ,  $\text{NRSO}_2\text{R}$ ,  $\text{NRSO}_2\text{NR}_2$ ,  $\text{OCONR}_2$ , CN, COOR,  $\text{CONR}_2$ , COR, or  $\text{R}_3\text{Si}$  wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, or

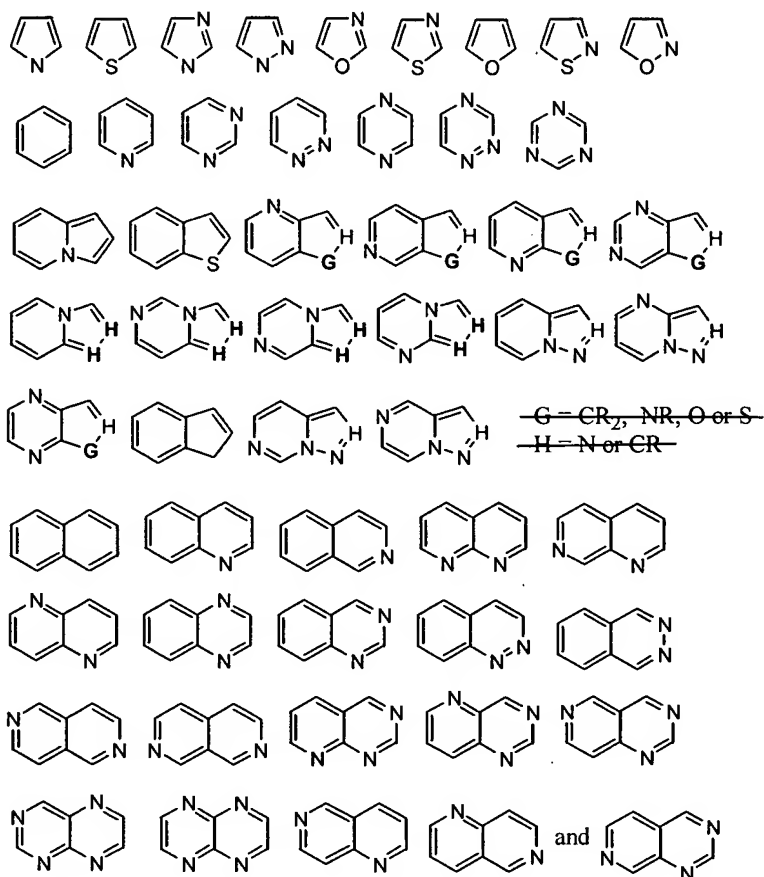
wherein  $\text{R}^3$  is OR,  $\text{NR}_2$ , SR,  $\text{NRCONR}_2$ ,  $\text{OCONR}_2$ , or  $\text{NRSO}_2\text{NR}_2$ , wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof, and wherein two R attached to the same atom may form a 3-8 member carbocyclic or heterocyclic ring and wherein said ring may further be substituted by alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroalkyl, heteroaryl, heteroarylalkyl, each optionally substituted with halo, SR, OR,  $\text{NR}_2$ , OCOR, NRCOR,  $\text{NRCONR}_2$ ,  $\text{NRSO}_2\text{R}$ ,  $\text{NRSO}_2\text{NR}_2$ ,  $\text{OCONR}_2$ , or  $\text{R}_3\text{Si}$  wherein each R is independently H, alkyl, alkenyl or aryl or the heteroatom-containing forms thereof wherein two R attached to the same atom may form a 3-8 member ring, optionally substituted as above defined; and

X, if present, is  $\text{CR}_2$  where R is as defined above.

4. (original): The compound of claim 1 wherein Y is an isostere of  $\text{COR}^3$ .

5. (original): The compound of claim 4 wherein Y is tetrazole; 1,2,3-triazole; 1,2,4-triazole; or imidazole.
6. (original): The compound of claim 1 wherein each of i and j is 0.
7. (original): The compound of claim 3 wherein j is 0.
8. (currently amended): The compound of claim 1 wherein  $-Ar^2-$  comprises an optionally substituted monocyclic or polycyclic aromatic nucleus, wherein said aromatic nucleus consists of carbocyclic or heterocyclic ring selected from (i) a five-membered heterocyclic or carbocyclic ring; (ii) a six-membered carbocyclic or heterocyclic ring; (iii) a five-membered carbocyclic or ~~heterocyclic~~ heterocyclic ring fused to another five-membered carbocyclic or heterocyclic ring; (iv) a six-membered carbocyclic or heterocyclic ring fused to another six-membered carbocyclic or heterocyclic ring; and (v) a five-membered heterocyclic or carbocyclic ring fused to a six-membered carbocyclic or heterocyclic ring.

9. (currently amended): The compound of claim 8 wherein  $\text{Ar}^2$  is selected from:

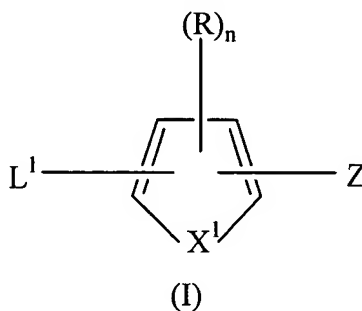


wherein  $\text{G}$  is  $\text{CR}_2$ ,  $\text{NR}$ ,  $\text{O}$  or  $\text{S}$ ; and

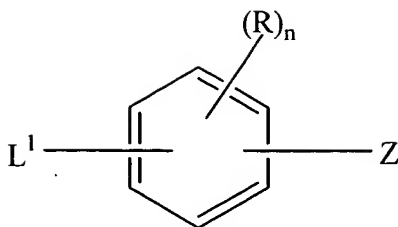
$\text{H}$  is  $\text{N}$  or  $\text{CR}$

~~[[where]]~~ wherein  $\text{R}$  is hydrogen or a noninterfering substituent.

10. (currently amended): The compound of claim 8 wherein the portion of said compound represented by  $\text{L}^1\text{-Ar}^2\text{-Z}$  is selected from the following:

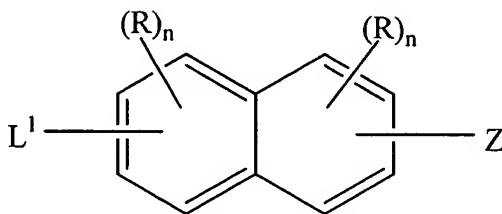


wherein  $n$  is 0, 1 or 2;  $\text{X}^1$  is  $\text{NR}$ ,  $\text{CR}_2$ ,  $\text{O}$  or  $\text{S}$ ; and each  $\text{R}$  is independently  $\text{H}$  or a noninterfering substituent; and two or more  $\text{R}$  groups may form a fused ring;



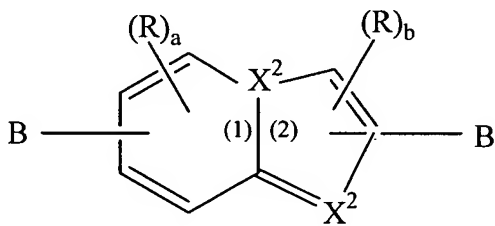
(II)

wherein n is 0-4; R is H or a noninterfering substituent where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



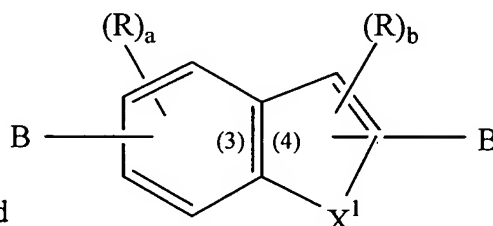
(III)

wherein each n is ~~independently~~ independently 0 to 3; R is H or a noninterfering substituent, where two or more R groups may form a fused ring; and one or more ring carbons may be optionally replaced with nitrogen;



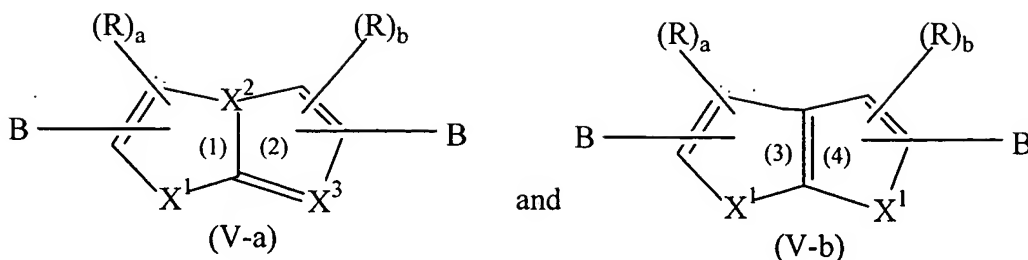
(IV-a)

and



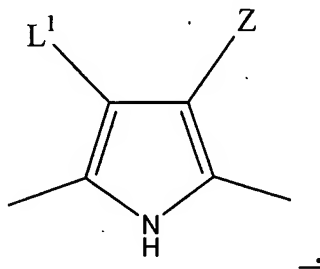
(IV-b)

wherein, subject to the proviso of claim 1, one B is L<sup>1</sup> and the other is Z; wherein a is 0 to 4 such that the positions on the six membered rings (1) and (3) to which (R)<sub>a</sub> is bonded can include X<sup>2</sup> when X<sup>2</sup> is C; b is 0-3 such that the positions on the five-membered rings (2) and (4) to which (R)<sub>b</sub> is bonded can include X<sup>2</sup> and X<sup>1</sup>, when X<sup>2</sup> is C and X<sup>1</sup> is N or C; each X<sup>2</sup> is independently N or CR; X<sup>1</sup> is NR, CR<sub>2</sub>, O or S; each R is H or a noninterfering substituent where two or more R groups may form a fused ring; wherein one or more of the ring carbons that are at positions other than X<sup>2</sup> or X<sup>1</sup> and that are also not bound to B can be optionally replaced with N;

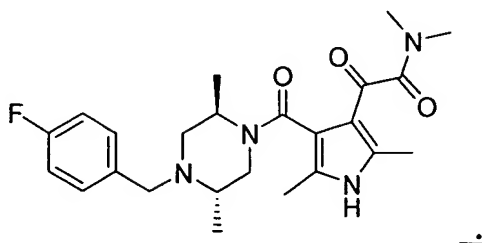


wherein one B is  $L^1$  and the other is Z; a is 0-4 such that the positions on the rings (1) and (3) to which  $(R)_a$  can be bonded include  $X^2$  and  $X^1$  where  $X^2$  is C and  $X^1$  is C or N; b is 0 or 3 such that the positions on the rings (2) and (4) to which  $(R)_b$  can be bonded include  $X^1$ ,  $X^2$  and  $X^3$  when  $X^1$  is C or N and  $X^2$  and/or  $X^3$  are C; each  $X^1$  is independently NR,  $C(R)_2$ , O or S;  $X^2$  and  $X^3$  are independently N or CR; each R is independently H or a noninterfering substituent where two or more R groups can optionally form a fused ring; wherein one or more of the ring carbons that are at positions other than  $X^1$ ,  $X^2$  or  $X^3$ , and that are also not bound to B, can be optionally replaced with N.

11. (original): The compound of claim 10 wherein  $L^1$ -Ar<sup>2</sup>-Z is structure (I).
12. (original): The compound of claim 11 wherein  $X^1$  in structure (I) is NR.
13. (original): The compound of claim 12 wherein  $X^1$  in structure (I) is NH.
14. (original): The compound of claim 13 wherein R is methyl.
15. (original): The compound of claim 14 wherein n is 2.
16. (currently amended): The compound of claim 15 wherein structure (I) is:

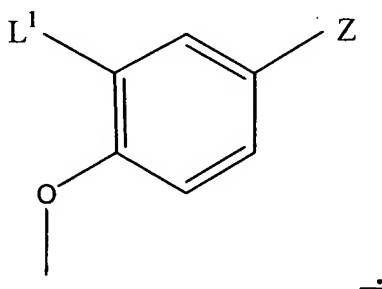


17. (currently amended): The compound of claim 16 where the compound is:



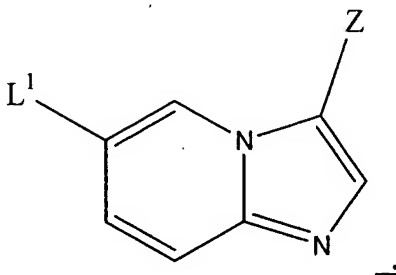
- [[140]] 18. (currently amended): The compound of claim 10 wherein  $L^1$ -Ar<sup>2</sup>-Z is structure (II).

19. (original): The compound of claim 18 wherein the R in structure (II) is methoxy.
20. (original): The compound of claim 19 wherein n in structure (II) is 1.
21. (currently amended): The compound of claim 20 wherein structure (II) is

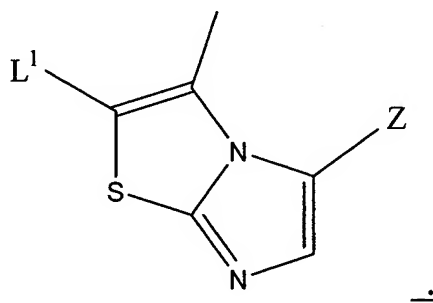


22. (canceled)
23. (original): The compound of claim 10 wherein  $L^1$ -Ar<sup>2</sup>-Z is structure (III).
24. (original): The compound of claim 10 wherein  $L^1$ -Ar<sup>2</sup>-Z is structure (IV-a) or (IV-b).
25. (original): The compound of claim 24 wherein  $L^1$ -Ar<sup>2</sup>-Z is (IV-a) and both X<sup>2</sup> in structure (IV-a) are nitrogen.

26. (currently amended): The compound of claim 25 wherein structure (IV) is:



27. (canceled)
28. (original): The compound of claim 8 wherein  $L^1$ -Ar<sup>2</sup>-Z is structure (V-a) or (V-b).
29. (original): The compound of claim 28 wherein  $L^1$ -Ar<sup>2</sup>-Z is structure (V-a) and X<sup>2</sup> and X<sup>3</sup> in structure (V-a) are N.
30. (original): The compound of claim 29 wherein at least one R in structure (V) is methyl.
31. (original): The compound of claim 29 wherein X<sup>1</sup> in structure (V) is S.
32. (currently amended): The compound of claim 31 wherein structure (V) is:



- 33-34. (canceled)

35. (original): The compound of claim 1 wherein L<sup>1</sup> is CO, CHOH or CH<sub>2</sub>.



36. (original): The compound of claim 35 wherein  $L^1$  is CO.

37-38. (canceled)

39. (currently amended): The compound of claim 1 wherein  $L^2$  is alkylene (1-4C) or alkenylene (1-4C) optionally substituted with a moiety selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR,  $NR_2$ , SR, SOR,  $SO_2R$ , OCOR, NRCOR,  $NRCONR_2$ ,  $NRCOOR$ ,  $OCONR_2$ , RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR,  $SO_3R$ ,  $CONR_2$ ,  $SO_2NR_2$ ,  $NRSO_2NR_2$ , CN,  $CF_3$ ,  $R_3Si$ , and  $NO_2$ , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two substituents on  $L^2$  can be joined to form a non-aromatic saturated or unsaturated ring that includes 0-3 heteroatoms which are O, S and/or N and which contains 3 to 8 members or said two substituents can be joined to form a carbonyl moiety or an oxime, oximeether, oximeester or ketal of said carbonyl moiety.

40. (original): The compound of claim 39 wherein  $L^2$  is unsubstituted alkylene.

41. (original): The compound of claim 39 wherein  $L^2$  is unsubstituted methylene, methylene substituted with alkyl, or  $-CH=$ .

42. (currently amended): The compound of claim 1 wherein  $Ar^1$  is optionally substituted with 0-5 substituents selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR,  $NR_2$ , SR, SOR,  $SO_2R$ , OCOR, NRCOR,  $NRCONR_2$ ,  $NRCOOR$ ,  $OCONR_2$ , RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR,  $SO_3R$ ,  $CONR_2$ ,  $SO_2NR_2$ ,  $NRSO_2NR_2$ , CN,  $CF_3$ ,  $R_3Si$ , and  $NO_2$ , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof, and wherein two of said optional substituents on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.

43. (original): The compound of claim 42 wherein  $Ar^1$  is optionally substituted phenyl.

44. (original): The compound of claim 43 wherein said optional substitution is by halo, OR, or alkyl.

45. (original): The compound of claim 44 wherein said phenyl is unsubstituted or has a single substituent.

46. (currently amended): The compound of claim 1 wherein  $R^1$  is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl, halo, OR,  $NR_2$ , SR, SOR,  $SO_2R$ , OCOR, NRCOR,  $NRCONR_2$ ,  $NRCOOR$ ,  $OCONR_2$ , RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR,  $SO_3R$ ,  $CONR_2$ ,  $SO_2NR_2$ ,  $NRSO_2NR_2$ , CN,  $CF_3$ ,  $R_3Si$ , and  $NO_2$ , wherein each R is independently H, alkyl, alkenyl or aryl or heteroforms thereof and two of  $R^4$  on adjacent positions can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members, or  $R^4$  is =O or an oxime, oximeether, oximeester or ketal thereof.

47. (original): The compound of claim 46 wherein each  $R^1$  is halo, OR, or alkyl.

48. (original): The compound of claim 47 wherein m is 0, 1, or 2.

49. (original): The compound of claim 48 wherein m is 2 and both  $R^1$  are alkyl.

50. (currently amended): The compound of claim 10 wherein each of the non-interfering groups R, when bonded to a ring carbon atom, are selected from the group consisting of:

(a) hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, acyl, aroyl, heteroaryl, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkylaryl, NH-aroyl and halo; or

(b) or from OR,  $NR_2$ , SR, SOR,  $SO_2R$ , OCOR, NRCOR,  $NRCONR_2$ ,  $NRCOOR$ ,  $OCONR_2$ , RCO, COOR, ~~alkyl-OOR~~ alkyl-OOCR,  $SO_3R$ ,  $CONR_2$ ,  $SO_2NR_2$ ,  $NRSO_2NR_2$ , CN,  $CF_3$ ,  $R_3Si$ , and  $NO_2$ , wherein each R in the preceding (b) selections is independently H, alkyl, alkenyl or aryl or heteroforms thereof;

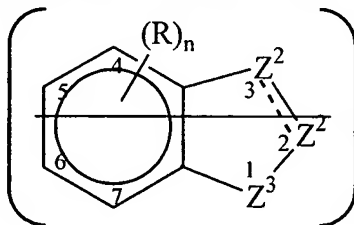
and wherein two of the non-interfering groups R can be joined to form a fused, optionally substituted aromatic or nonaromatic, saturated or unsaturated ring which contains 3-8 members.



Z is  $-W_i-CO-X_j-Y$  wherein Y is  $COR^3$  or an isostere thereof;  $R^3$  is a noninterfering substituent; each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of  $Ar^1$  bonded to  $L^2$  to the atom of  $Ar^2$  bonded to  $L^1$  is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of  $Ar^1$  bonded to  $L^2$  and the atom of  $Ar^2$  bonded to  $L^1$  is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by  $Ar^2-Z$  is not



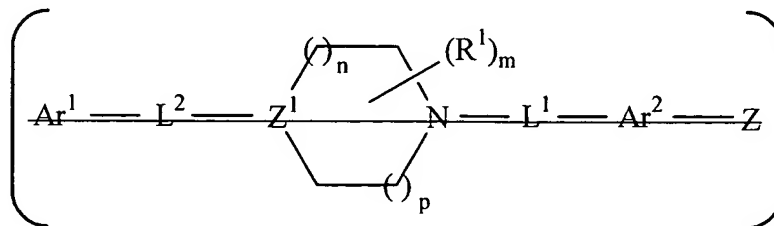
wherein  $\text{---}\diagup\diagdown\text{---}$  represents a single or double bond; n is 0-3; one  $Z^2$  is CA or CRA and the other is CR,  $CR_2$ , NR or N; A is  $-W_i-CO-X_j-Y$  wherein Y is  $COR$  or an isostere thereof, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;  $Z^3$  is NR or O; and each R is independently hydrogen or a noninterfering substituent.

54. (canceled)

55. (original): The composition of claim 53 which further contains an additional therapeutic agent.

56. (original): The composition of claim 55 wherein said additional therapeutic agent is a corticosteroid, a monoclonal antibody, or an inhibitor of cell division.

57. (currently amended): A method to treat a condition mediated by p38- $\alpha$  kinase comprising administering to a subject in need of such treatment a compound of claim 1 the formula:



and the pharmaceutically acceptable salts thereof, or a pharmaceutical composition thereof, wherein

$\text{Ar}^1$  is an aryl group substituted with 0-5 non-interfering substituents, wherein two adjacent noninterfering substituents can form a fused aromatic or nonaromatic ring;

$\text{L}^1$  and  $\text{L}^2$  are linkers;

each  $\text{R}^1$  is independently a noninterfering substituent;

$\text{Z}^1$  is  $\text{CR}^2$  or N wherein  $\text{R}^2$  is hydrogen or a noninterfering substituent;

m is 0-4;

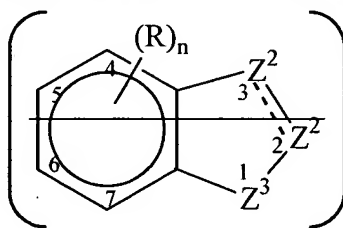
each of n and p is an integer from 0-2 wherein the sum of n and p is 0-3;

$\text{Ar}^2$  is a substantially planar, monocyclic or polycyclic aromatic moiety having one or more optional ring heteroatoms, said moiety being optionally substituted with one or more non-interfering substituents, two or more of which may form a fused ring;

Z is  $\text{W}_i\text{COX}_j\text{Y}$  wherein Y is  $\text{COR}^3$  or an isostere thereof;  $\text{R}^3$  is a noninterfering substituent, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;

wherein the smallest number of covalent bonds in the compound separating the atom of  $\text{Ar}^1$  bonded to  $\text{L}^2$  to the atom of  $\text{Ar}^2$  bonded to  $\text{L}^1$  is at least 6, where each of said bonds has a bond length of 1.2 to 2.0 angstroms; and/or wherein the distance in space between the atom of  $\text{Ar}^1$  bonded to  $\text{L}^2$  and the atom of  $\text{Ar}^2$  bonded to  $\text{L}^1$  is 4.5-24 angstroms;

with the proviso that the portion of the compound represented by  $\text{Ar}^2\text{-Z}$  is not



wherein  $\text{---}\text{Z}\text{---}$  represents a single or double bond; n is 0-3; one  $\text{Z}^2$  is CA or CRA and the other is CR,  $\text{CR}_2$ , NR or N; A is  $\text{W}_i\text{COX}_j\text{Y}$  wherein Y is COR or an isostere thereof, each of W and X is a spacer of 2-6 Å, and each of i and j is independently 0 or 1;  $\text{Z}^3$  is NR or O; and each R is independently hydrogen or a noninterfering substituent.

58. (canceled)

59. (original): The method of claim 57 wherein said condition is a proinflammation response.

60. (currently amended): The method of claim 59 wherein said proinflammation response is multiple sclerosis, IBD, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, other arthritic conditions, sepsis, ~~septic shock~~, endotoxic shock, ~~Gram-negative sepsis~~, ~~toxic shock syndrome~~, asthma, adult respiratory distress syndrome, ~~[[stroke,]]~~ reperfusion injury, ~~CNS injury~~, psoriasis, ~~restenosis~~, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, a bone resorption disease, graft-versus-host reaction, Crohn's Disease, ulcerative colitis, ~~Alzheimer's~~, or pyresis ~~or heart disease~~.